

This listing of claims will replace all prior versions of claims in the application.

Claim 1. (Currently amended) A formulation comprising penetrants being capable of penetrating the pores of a barrier, the average diameter of said pores being smaller than the average diameter of said penetrants, wherein said penetrants can transport agents or enable agent penetration through said pores after said penetrants have entered said pores, wherein the formulation further comprises

1) at least one antioxidant in an amount that reduces the increase of oxidation index to less than 100% per 6 months; and

2) at least one microbiocide in an amount that reduces the bacterial count of 1 million germs added per gram of total mass of the formulation to less than 100 in the case of aerobic bacteria, to less than 10 in the case of entero-bacteria, and to less than 1 in the case of *Pseudomonas aeruginosa* or *Staphylococcus aureus*, after a period of 4 days;

wherein the agent is selected from corticosteroids and the relative content of corticosteroids is above 0.1 weight-%, relative to total dry mass of the formulation.

Claim 2. (previously presented) The formulation according to claim 5, wherein said at least one consistency builder is added in an amount that increases the formulation viscosity to up to  $1 \text{ Ns/m}^2$ .

Claim 3. (previously presented) The formulation according to claim 1, wherein said at least one antioxidant is added in an amount that reduces the increase of oxidation index to less than 100% per 12 months.

Claim 4. (cancelled)

Claim 5. (previously presented) The formulation according to claim 1, further comprising at least one consistency builder, in an amount that increases the formulation viscosity

above that of the non-thickened corresponding formulation to maximally  $5 \text{ Ns/m}^2$  so that spreading over, and retention at, the application area is enabled.

Claim 6. (previously presented) The formulation according to claim 83, wherein the polymer weight fractions are in the range between 0.05% and 10%.

Claims 7-8. (cancelled)

Claim 9. (previously presented) The formulation according to claim 1, further comprising at least one microbiocide in an amount that reduces the bacterial count of 1 million germs added per gram of total mass of the formulation to less than 100 in the case of aerobic bacteria, to less than 10 in the case of entero-bacteria, and to less than 1 in the case of *Pseudomonas aeruginosa* or *Staphylococcus aureus*, after a period of 4 days.

Claims 10-11. (cancelled)

Claim 12. (previously presented) The formulation according to claim 1, further comprising at least one consistency builder or at least one anti-oxidant or at least one microbiocide and mixtures thereof.

Claim 13. (previously presented) The formulation according to claim 1, wherein the corticosteroid is selected from the group consisting of: alclonetasone dipropionate, amcinonide, beclomethasone dipropionate, betamethasone, betamethasone 17-valerate, betamethasone 17,21-divalate, betamethasone 21-acetate, betamethasone 21-butyrate, betamethasone 21-propionate, betamethasone 21-valerate, betamethasone benzoate, betamethasone dipropionate, betamethasone valerate, budesonide, clobetasol propionate, clobetasone butyrate, cortexolone, corticosterone, cortisone, cortisone 17-acetate, 21-deoxybetamethasone, 21-deoxybetamethasone 17-propionate, deoxycorticosterone, desonide, desoxymethasone, dexamethasone, diflorasone

diacetate, diflucortolone valerate, flucolorolone acetonide, flumethasone pivalate, fluoconolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, 9-alpha-fluorocortisone, 9-alpha-fluorohydrocortisone, 9-alpha-fluoroprednisolone, fluprednidene acetate, flurandrenolone, halcinonide, hydrocortisone, hydrocortisone 17-acetate, hydrocortisone 17-butyrate, hydrocortisone 17-propionate, hydro cortisone 17-valerate, hydrocortisone 21-acetate, hydrocortisone 21-butyrate, hydrocortisone 21-propionate, hydrocortisone 21-valerate, 17-alpha-hydroxyprogesterone, methylprednisolone acetate, mometasone furoate, prednisolone, prednisone, prednisone 17-acetate, prednisone 17-valerate, progesterone, triamcinolone, and trimcinolone acetonide.

Claim 14. (previously presented) The formulation according to claim 1, wherein the penetrants are suspended or dispersed in a polar liquid in the form of fluid droplets surrounded by a membrane-like coating of one or several layers, said coating comprising at least two kinds or forms of amphiphilic substances with a tendency to aggregate,

wherein said at least two substances differ by at least a factor of 10 in solubility in said liquid or wherein said substances when in the form of homo-aggregates, for the more soluble substance, or of hetero-aggregates, for any combination of both said substances, have preferred average diameter smaller than the diameter of the homo-aggregates containing merely the less soluble substance; or

wherein the presence of the more soluble substance lowers the average elastic energy of the membrane-like coating in the vicinity of thermal energy.

Claims 15-20. (cancelled)

Claim 21. (previously presented) The formulation according to claim 14, wherein the average penetrant diameter is between 30 nm and 500 nm.

Claim 22. (previously presented) The formulation according to claim 14, wherein the average diameter of the penetrant is 2 to 25 times bigger than the average diameter of the pores in the barrier.

Claim 23. (previously presented) The formulation according to claim 14, wherein the dry weight of all carrier droplets in a formulation for the use on human or animal skin is 0.01 weight-% (w-%) to 40w-% of total formulation mass.

Claim 24. (previously presented) The formulation according to claim 14, wherein the dry weight of all carrier droplets in a formulation for the use on human or animal mucosa is 0.0001 w-% to 30 w-% of total formulation mass.

Claims 25-34. (cancelled)

Claim 35. (previously presented) The formulation according to claim 1, wherein the content of corticosteroids is between 0.1 w-% and 20 w-%.

Claims 36-38. (cancelled)

Claim 39. (previously presented) The formulation according to claim 35, wherein the relative content of corticosteroids is the case of clobetasol or one of its derivatives is below 15 w-%, relative to total dry mass of the drug-loaded carriers.

Claim 40. (previously presented) The formulation according to claim 35, wherein the content of said corticosteroid is below the saturation maximum, defined as the content of corticosteroid at which the corticosteroid begins to crystallize in or outside the carrier.

Claim 41. (previously presented) The formulation according to claim 1, wherein in order

to speed up drug action a permeation enhancer is added.

Claims 42–43. (cancelled)

Claim 44. (previously presented) The formulation according to claim 1, wherein said corticosteroid is added in an amount which enables the formulation to be applied corresponding to an area dose, as expressed by the total dry mass of penetrant applied per unit area, of between  $0.1 \text{ mg cm}^{-2}$  and  $15 \text{ mg cm}^{-2}$ , if said corticosteroid is desired to exert a therapeutic effect in the deep subcutaneous tissue or the remote tissues, including the whole body.

Claim 45. (previously presented) The formulation according to claim 1, wherein said corticosteroid is added in an amount which enables the formulation to be applied with an area dose, as expressed by the total dry mass of penetrant applied per unit area, of between  $1 \text{ } \mu\text{g cm}^{-2}$  and  $250 \text{ } \mu\text{g cm}^{-2}$ , if said corticosteroid is desired to exert a mainly local rather than systemic therapeutic effect.

Claim 46. (previously presented) The formulation according to claim 1, wherein consistency and, if necessary other characteristics of the formulation are appropriately selected to enable spraying, smearing, rolling or sponging of the formulation on the application area in particular by using a sprayer, spender, roller or sponge.

Claims 47–50. (cancelled)

Claim 51. (previously presented) The formulation according to claim 83, wherein the pharmaceutically acceptable hydrophilic polymers are selected from partially etherified cellulose derivatives, comprising carboxymethyl-, hydroxyethyl-, hydroxypropyl-, hydroxypropylmethyl-, or methyl-cellulose.

Claim 52. (previously presented) The formulation according to claim 83, wherein the completely synthetic hydrophilic polymers are selected from polyacrylates, polymethacrylates, poly(hydroxyethyl)-, poly(hydroxypropyl)-, poly(hydroxypropylmethyl)methacrylate, polyacrylonitrile, methallyl-sulphonate, polyethylenes, polyoxiethylenes, polyethylene glycols, polyethylene glycol-lactide, polyethylene glycol-diacrylate, polyvinylpyrrolidone, polyvinyl alcohols, poly(propylmethacrylamide), poly(propylene fumarate-co-ethylene glycol), poloxamers, polyaspartamide, hyaluronic acid, hydrazine cross-linked hyaluronic acid and silicone.

Claim 53. (previously presented) The formulation according to claim 83, wherein the natural gums are selected from alginates, carrageenan, guar-gum, gelatine, tragacanth, pectin, amidated pectin, xanthan, chitosan collagen and agarose.

Claim 54. (Previously presented) The formulation according to claim 84, wherein the synthetic phenolic antioxidants are selected from butylated hydroxyanisol (BHA), butylated hydroxytoluene (BHT) and di-tert-butylphenol (LY178002, LY256548, HWA-131, BF-389, CI-986, PD-127443, E-5119, BI-L-239XX), tertiary butylhydroquinone (TBHQ), propyl gallate (PG) and 1-O-hexyl-2,3,5-trimethylhydroquinone (HTHQ).

Claim 55. (Previously presented) The formulation according to claim 84, wherein the aromatic amines are selected from diphenylamine, p-alkylthio-o-anisidine, ethylenediamine derivatives, carbazol and tetrahydroindenoindol.

Claim 56. (previously presented) The formulation according to claim 84, wherein the phenols and phenolic acids are selected from guaiacol, hydroquinone, vanillin, gallic acids and their esters, protocatechuic acid, quinic acid, syringic acid, ellagic acid, salicylic acid, nordihydroguaiaretic acid (NDGA) and eugenol.

Claim 57. (previously presented) The formulation according to claim 84, wherein the

tocopherols and their derivatives are selected from tocopheryl-acylate, -laurate, myristate, -palmitate, -oleate, -linoleate, or any other suitable tocopheryl-lipoate and tocopheryl-POE-succinate.

Claim 58. (previously presented) The formulation according to claim 84, wherein the ascorbic acids are selected from 6-o-lauroyl, myristoyl, palmitoyl-, oleoyl, or linoleoyl-L-ascorbic acid.

Claim 59. (previously presented) The formulation according to claim 84, wherein the non-steroidal anti-inflammatory agents (NSAIDs) are selected from indomethacine, diclofenac, mefenamic acid, flufenamic acid, phenylbutazone, oxyphenbutazone acetylsalicylic acid, naproxen, diflunisal, ibuprofene, ketoprofene, piroxicam, penicillamine, penicillamine disulphide, primaquine, quinacrine, chloroquine, hydroxychloroquine, azathioprine, phenobarbital and acetaminophen.

Claim 60. (previously presented) The formulation according to claim 84, wherein the antiarrhythmics are selected from amiodarone, aprindine and asocainol.

Claim 61. (previously presented) The formulation according to claim 84, wherein the calcium antagonists are selected from nifedipine, nisoldipine, nimodipine, nicardipine and nilvadipine.

Claim 62. (previously presented) The formulation according to claim 84, wherein the beta-receptor blockers are selected from atenolol, propranolol and nebivolol.

Claim 63. (previously presented) The formulation according to claim 84, wherein the chellating agents are selected from EDTA, GDTA and desferral.

Claim 64. (previously presented) The formulation according to claim 84, wherein the miscellaneous endogenous defense systems are selected from transferrin, lactoferrin, ferritin, ceruloplasmin, haptoglobin, haemopexin, albumin, glucose and ubiquinol-10.

Claim 65. (previously presented) The formulation according to claim 84, wherein the enzymatic antioxidants is superoxide dismutase.

Claim 66. (previously presented) The formulation according to claim 84, wherein the metal complexes are selected from catalase and glutathione peroxidase.

Claim 67. (previously presented) The formulation according to claim 84, wherein the less complex molecules are selected from beta-carotene, bilirubin and uric acid.

Claim 68. (previously presented) The formulation according to claim 84, wherein the flavonoids are selected from flavones, flavonols, flavonones, flavanones, chalcones and anthocyanins.

Claim 69. (previously presented) The formulation according to claim 84, wherein the tannins, cinnamic acid, hydroxycinnamic acids and their esters are selected from coumaric acid and esters, caffeic acid and their esters, ferulic acid, (iso-)chlorogenic acid and sinapic acid.

Claim 70. (previously presented) The formulation according to claim 84, wherein the spice extracts are selected from spice extracts from clove, cinnamon, sage, rosemary, mace, oregano, allspice and nutmeg.

Claim 71. (previously presented) The formulation according to claim 84, wherein the oat flour extract is avenanthramide 1 or 2.



Claim 72. (previously presented) The formulation according to claim 84, wherein the steroid derivative is U74006F.

Claim 73. (previously presented) The formulation according to claim 84, wherein the tryptophan metabolites are selected from 3-hydroxykynurenine and 3-hydroxyanthranilic acid.

Claim 74. (previously presented) The formulation according to claim 85, wherein the short chain alcohols are selected from ethyl and isopropyl alcohol, chlorobutanol, benzyl alcohol, chlorobenzyl alcohol, dichlorobenzylalcohol and hexachlorophene.

Claim 75. (previously presented) The formulation according to claim 85, wherein the phenolic compounds are selected from cresol, 4-chloro-m-cresol, p-chloro-m-xenol, dichlorophene, hexachlorophene and povidon-iodine.

Claim 76. (previously presented) The formulation according to claim 85, wherein the parabenes are selected from alkyl-parabenes, including methyl-, ethyl-, propyl-, or butyl- paraben and benzyl paraben.

Claim 77. (previously presented) The formulation according to claim 85, wherein the acids are selected from sorbic acid, benzoic acid and their salts.

Claim 78. (previously presented) The formulation according to claim 85, wherein the quaternary ammonium compounds are selected from alkonium salts, benzalkonium salts, cetrimonium salts, phenoalkecinium salts, phenododecinium bromide, cetylpyridinium chloride and other salts.

Claim 79. (previously presented) The formulation according to claim 78, wherein the benzalkonium salts are selected from benzalkonium chloride and benzalkonium bromide.

Claim 80. (previously presented) The formulation according to claim 85, wherein the mercurial compounds are selected from phenylmercuric acetate, borate, or nitrate, thiomersal, chlorhexidine or its gluconate, and mixtures thereof.

Claim 81. (previously presented) The formulation of claim 1, wherein the corticosteroids are selected from glucocorticoids or mineralocorticosteroids.

Claim 82. (previously presented) The formulation according to claim 39, wherein the corticosteroid is propionate.

Claim 83. (previously presented) The formulation according to claim 5, wherein the consistency builder is selected from the group consisting of:

pharmaceutically acceptable hydrophilic polymers; completely synthetic hydrophilic polymers; natural gums; and mixtures and further derivatives or co-polymers thereof.

Claim 84. (previously presented) The formulation according to claim 1, wherein the anti-oxidant is selected from the group consisting of:

synthetic phenolic antioxidants; aromatic amines; phenols and phenolic acids; tocopherols and their derivatives; trolox and corresponding amide and thiocarboxamide analogues; ascorbic acid and its salts, isoascorbate, (2 or 3 or 6)-o-alkylascorbic acids, ascorbyl esters; non-steroidal anti-inflammatory agents (NSAIDs); aminosalicic acids and derivatives; methotrexate, probucol, antiarrhythmics; ambroxol, tamoxifene, b-hydroxytamoxifene; calcium antagonists, beta-receptor blockers; sodium bisulphite, sodium metabisulphite, thiourea; chellating agents; miscellaneous endogenous defense systems; enzymatic antioxidants and metal complexes with a similar activity, and less complex molecules; flavonoids; N-acetylcystein,

mesna, glutathione, thiohistidine derivatives, triazoles; tannines, cinnamic acid, hydroxycinnamic acids and their esters; spice extracts; carnosic acid, carnosol, carsolic acid; rosmarinic acid, rosmaridiphenol, gentisic acid, ferulic acid; oat flour extracts; thioesters, dithioesters, sulphoxides, tetralkylthiuram disulphides; phytic acid, steroid derivatives; and tryptophan metabolites and organochalcogenides.

Claim 85. (previously presented) The formulation according to claim 9, wherein the microbiocide is selected from the group consisting of:

short chain alcohols; phenolic compounds; parabenes; acids and their salts; quaternary ammonium compounds and other salts; mercurial compounds; and mixtures thereof.